Squibb—Cont.

water, or that any discoloration of fabrics from the Ointment may be removed by applying a standard cleaning fluid.

How Supplied: Fungizone Cream (Amphotericin B Cream USP) is supplied in tubes of 20 grams.

Fungizone Lotion (Amphotericin B Lotion USP) is supplied in 30 ml. plastic squeeze bottles (Military Depot Item, NSN 6505-00-890-1486).

Fungizone Ointment (Amphotericin B Ointment USP) is supplied in tubes of 20 grams.

Storage: Store the Cream and Lotion at room temperature; avoid freezing. Store the Ointment at room temperature.

FUNGIZONE® INTRAVENOUS
(Amphotericin B for Injection USP)

WARNING

This drug should be used *primarily* for treatment of patients with progressive and potentially fatal fungal infections; it should not be used to treat the common clinically inapparent forms of fungal disease which show only positive skin or serologic tests.

Description: Fungizone Intravenous (Amphotericin B for Injection USP) is an antifungal antibiotic derived from a strain of *Streptomyces nodosus*. Crystalline amphotericin B is insoluble in water; therefore, the antibiotic is "solubilized" by the addition of sodium desoxycholate to form a mixture which provides a colloidal dispersion for parenteral administration.

Actions:

Microbiology

Amphotericin B shows a high order of *in vitro* activity against many species of fungi. *Histoplasma capsulatum, Coccidiodes immitis, Candida* species, *Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporotrichum schenckii, Mucor mucedo,* and *Aspergillus fumigatus* are all inhibited by concentrations of amphotericin B ranging from 0.03 to 1.0 mcg./ml. *in vitro*. The antibiotic is without effect on bacteria, rickettsiae, and viruses.

Clinical Pharmacology

Amphotericin B is fungistatic or fungicidal depending on the concentration obtained in body fluids and the susceptibility of the fungus. The drug probably acts by binding to sterols in the fungus cell membrane with a resultant change in membrane permeability which allows leakage of a variety of small molecules. Mammalian cell membranes also contain sterols and it has been suggested that the damage to human cells and fungal cells may share common mechanisms.

An initial intravenous infusion of 1 to 5 mg. of amphotericin B per day, gradually increased to 0.65 mg./kg. daily, produces peak plasma concentrations of approximately 2 to 4 mcg./ml. which can persist between doses since the plasma half-life of amphotericin B is about 24 hours. (For recommended dosages, see the DOSAGE AND ADMINISTRATION section.)

It has been reported that amphotericin B is highly bound (>90%) to plasma proteins and is poorly dialyzable.

Amphotericin B is excreted very slowly by the kidneys with two to five percent of a given dose being excreted in biologically active form. After treatment is discontinued, the drug can be detected in the urine for at least seven weeks. The cumulative urinary output over a seven-day period amounts to approximately 40 percent of the amount of drug infused.

Details of tissue distribution and possible metabolic pathways are not known.

Indications: Fungizone Intravenous should be administered primarily to patients with progressive, potentially fatal infections. This potent drug should not be used to treat the common inapparent forms of fungal disease which show only positive skin or serologic tests.

Fungizone Intravenous (Amphotericin B for Injection USP) is specifically intended to treat cryptococcosis (torulosis); North American blastomycosis; the disseminated forms of moniliasis, coccidioidomycosis, and histoplasmosis; mucormycosis (phycomycosis) caused by species of the genera *Mucor, Rhizopus, Absidia, Entomophthora,* and *Basidiobolus;* sporotrichosis (*Sporothrix schenckii* [formerly *Sporotrichum schenckii*]); aspergillosis (*Aspergillus fumigatus*).

Amphotericin B may be helpful in the treatment of American mucocutaneous leishmaniasis, but is not the drug of choice in primary therapy.

Contraindications: This product is contraindicated in those patients who have shown hypersensitivity to it unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to amphotericin B therapy.

Warnings: Amphotericin B is frequently the only effective treatment available for potentially fatal fungal disease. In each case, its possible life-saving benefit must be balanced against its untoward and dangerous side effects.

Usage in Pregnancy: Safety for use in pregnancy has not been established; therefore, it should be used during pregnancy only if the possible benefits to be derived outweigh the potential risks involved.

Precautions: Prolonged therapy with amphotericin B is usually necessary. Unpleasant reactions are quite common when the drug is given parenterally at therapeutic dosage levels. **Some of these reactions are potentially dangerous.** Hence, amphotericin B should be used parenterally only in hospitalized patients or those under close clinical observation by medically trained personnel and should be reserved for those patients in whom a diagnosis of the progressive, potentially fatal forms of susceptible mycotic infections has been firmly established, preferably by positive culture or histologic study.

Corticosteroids should not be administered concomitantly unless they are necessary to control drug reactions. Other nephrotoxic antibiotics and antineoplastic agents such as nitrogen mustard should not be given concomitantly except with great caution.

Laboratory facilities must be available to perform blood urea nitrogen and serum creatinine or endogenous creatinine clearance tests. These determinations should be made at least weekly during therapy. If the BUN exceeds 40 mg. per 100 ml. or the serum creatinine exceeds 3.0 mg. per 100 ml. the drug should be discontinued or the dosage markedly reduced until renal function is improved. Weekly hemograms and serum potassium determinations are also advisable. Low serum magnesium levels have also been noted during treatment with amphotericin B. Therapy should be discontinued if liver function test results (elevated bromsulphalein, alkaline phosphatase and bilirubin) are abnormal.

Whenever medication is interrupted for a period longer than seven days, therapy should be resumed by starting with the lowest dosage level, e.g., 0.25 mg./kg. of body weight, and increased gradually as outlined under DOSAGE AND ADMINISTRATION.

Adverse Reactions: While some few patients may tolerate full intravenous doses of amphotericin B without difficulty, most will exhibit some intolerance, often at less than the full therapeutic dosage. They may be made less severe by giving aspirin, antihistamines, and antiemetics. Administration of the drug on alternate days may decrease anorexia and phlebitis. Intravenous administration of small doses of adrenal corticosteroids just prior to or during the amphotericin B infusion [illegible] crease febrile reactions. The dosage [illegible] tion of such corticosteroid therapy [illegible] kept to a minimum. Adding a small [illegible] heparin to the infusion may lessen [illegible] dence of thrombophlebitis. Extravasation [illegible] cause chemical irritation.

The adverse reactions that are most [illegible] observed are: fever (sometimes with [illegible] chills); headache; anorexia; weight loss; [illegible] and vomiting; malaise; dyspepsia; [illegible] generalized pain including muscle [illegible] pains, cramping epigastric pain, and [illegible] nous pain at the injection site with [illegible] and thrombophlebitis; and normochromic [illegible] mocytic anemia. Abnormal renal [illegible] cluding hypokalemia, azotemia, hypo[illegible] ria, renal tubular acidosis and nephro[illegible] sis is also commonly observed, and usually [illegible] proves upon interruption of therapy; [illegible] some permanent impairment often [illegible] especially in those patients receiving [illegible] amounts (over 5 g.) of amphotericin B. [illegible] mental alkali medication may decrease [illegible] tubular acidosis complications.

The following adverse reactions occur less [illegible] quently or rarely: anuria; oliguria; cardiac [illegible] cular toxicity including arrhythmias, ventricular fibrillation, cardiac arrest, hypertension and hypotension; coagulation defects; thrombocytopenia; leukopenia; agranulocytosis; eosinophilia; leukocytosis; melena or hemorrhagic gastroenteritis; maculopapular rash; hearing loss; tinnitus; transient visual blurred vision or diplopia; peripheral neuropathy; convulsions and other neurologic symptoms; pruritus (without rash); anaphylactic reactions; acute liver failure; and flushing.

Dosage and Administration: Fungizone Intravenous (Amphotericin B for Injection USP) should be administered by *slow* intravenous infusion. Intravenous infusion should be given over a period of approximately six hours, observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0.1 mg./ml. (1 mg./10 ml.).

Dosage must be adjusted to the specific requirements of each patient since tolerance to amphotericin B varies individually. Therapy is usually instituted with a daily dose of 0.25 mg./kg. of body weight and gradually increased as tolerance permits. There are insufficient data presently available to define optimum dosage requirements and duration of treatment necessary for eradication of various infections such as phycomycosis. The optimal dosage is not known. Total daily dosage may range from 0.25 mg./kg. of body weight or alternate day dosages ranging up to 1.5 mg./kg. Several weeks or months of therapy are usually necessary; however, a longer period of therapy may produce an increased clinical response and lead to relapse.

CAUTION: Under no circumstances should a total daily dosage of 1.5 mg./kg. be exceeded.

Therapy with intravenous amphotericin B for sporotrichosis has ranged up to nine months. The usual dose per injection is 20 mg. Aspergillosis has been treated with amphotericin B intravenously for a period of two months with a total dose up to 3.6 g.

Rhinocerebral phycomycosis, a fulminating disease, generally occurs in association with diabetic ketoacidosis. It is, therefore, imperative that rapid restoration of diabetic control be instituted before successful treatment of the infection can be accomplished.

Fungizone Intravenous (Amphotericin B for Injection USP) can be accomplished by [illegible] distinction, pulmonary phycomycosis [illegible] more common in association with [illegible] malignancies, is often an incidental finding at autopsy. A cumulative dose of at least 2 g. of amphotericin B is recommended. After a total dose of 3 to 4 g. will infrequently result in long-lasting renal impairment, this would be a reasonable minimum where there is no evidence of invasion of the deep tissues

Squibb—Cont.

cultures should be obtained from the original site(s) of infection 7 to 14 days after therapy. In women, it is also desirable to obtain culture test-of-cure from both the endocervical and anal canals. Note: gonorrheal endocarditis should be treated intensively with aqueous penicillin G.

Yaws, Bejel, and Pinta—treat same as syphilis in corresponding stage of disease.

Diphtheria—*adjunctive therapy with antitoxin:* 300,000 to 600,000 u. daily; **Anthrax**—cutaneous: 600,000 to 1,200,000 u. daily; **Rat-bite fever** (*S. moniliformis* and *S. minus*) and **Erysipeloid:** 600,000 to 1,200,000 u. daily.

Bacterial endocarditis (group A streptococcus) —only in extremely susceptible infections: 600,000 to 1,200,000 u. daily.

Prophylaxis against bacterial endocarditis—For prophylaxis against bacterial endocarditis[1] in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, use a combined parenteral-oral regimen. One million units of aqueous crystalline penicillin G (30,000 u./kg. in children) mixed with 600,000 u. of penicillin G procaine (600,000 u. for children) should be given intramuscularly one-half to one hour before the procedure. Oral penicillin V (phenoxymethyl penicillin), 500 mg. for adults or 250 mg. for children less than 60 lb., should be given every six hours for eight doses. Doses for children should not exceed recommendations for adults for a single dose or for a 24-hour period.

How Supplied: Crysticillin 300 A.S. (Sterile Penicillin G Procaine Suspension USP) is available in 10 ml. vials; Crysticillin 600 A.S. is available in 12 ml. vials.

Storage: Store below 15° C. (59° F.); avoid freezing.

Reference: 1. American Heart Association. 1977. Prevention of bacterial endocarditis. Circulation 56:139A-143A.

FUNGIZONE®
(Amphotericin B) B
CREAM/LOTION/OINTMENT

Description: Fungizone Cream (Amphotericin B Cream USP) contains the antifungal antibiotic Amphotericin B USP at a concentration of 3% (30 mg./gram) in a pleasantly tinted aqueous vehicle, which also contains titanium dioxide, thimerosal, propylene glycol, cetearyl alcohol (and) ceteareth-20, white petrolatum, methylparaben, propylparaben, sorbitol solution, glyceryl monostearate, polyethylene glycol monostearate, simethicone, and sorbic acid.

Fungizone Lotion (Amphotericin B Lotion USP) contains the antifungal antibiotic Amphotericin B USP at a concentration of 3% (30 mg./ml.) in a tinted aqueous lotion vehicle, which is pleasantly scented, and also contains thimerosal, titanium dioxide, guar gum, propylene glycol, cetyl alcohol, stearyl alcohol, sorbitan monopalmitate, polysorbate 20, glyceryl monostearate, polyethylene glycol monostearate, simethicone, sorbic acid, methylparaben, and propylparaben.

Fungizone Ointment (Amphotericin B Ointment USP) contains the antifungal antibiotic Amphotericin B USP at a concentration of 3% (30 mg./gram) in a tinted form of Plastibase® (Plasticized Hydrocarbon Gel), a polyethylene and mineral oil gel base with titanium dioxide.

Clinical Pharmacology: Amphotericin B is an antibiotic with antifungal activity which is produced by a strain of *Streptomyces nodosus*. It has been shown to exhibit greater *in vitro* activity than nystatin against *Candida* (Monilia) *albicans*. In clinical studies involving cutaneous and mucocutaneous candidal infections, results with topical preparations of amphotericin B were comparable to those obtained with nystatin in similar formulations.

Although amphotericin B exhibits some *in vitro* activity against the superficial dermatophytes (ringworm organisms), it has not demonstrated an effectiveness *in vivo* on topical application. Amphotericin B has no significant effect either *in vitro* or clinically against gram-positive or gram-negative bacteria, or viruses.

Indications and Usage: Fungizone (Amphotericin B) topical preparations are indicated in the treatment of cutaneous and mucocutaneous mycotic infections caused by Candida (Monilia) species.

Contraindications: The preparations are contraindicated in patients with a history of hypersensitivity to any of their components.

Precautions: Should a reaction of hypersensitivity occur the drug should be immediately withdrawn and appropriate measures taken.

Adverse Reactions: Fungizone Cream (Amphotericin B Cream USP)—No evidence of any systemic toxicity or side effects has been observed during or following the use of the Cream. The preparation is usually well tolerated by all age groups. It is not a primary irritant and apparently has only a slight sensitizing potential. It may have a "drying" effect on some skin, and local irritation characterized by erythema, pruritus, or a burning sensation sometimes occurs, particularly in intertriginous areas.

Fungizone Lotion (Amphotericin B Lotion USP)—No evidence of any systemic toxicity or side effects has been observed during or following even prolonged, intensive and extensive application of the Lotion. The preparation is extremely well tolerated by all age groups, including infants, even when therapy must be continued for many months. It is not a primary irritant and apparently has only a slight sensitizing potential. Local intolerance, which seldom occurs, has included increased pruritus with or without other subjective or objective evidence of local irritation, or exacerbation of preexisting candidal lesions. Allergic contact dermatitis is rare.

Fungizone Ointment (Amphotericin B Ointment USP)—No evidence of any systemic toxicity or side effects has been observed during or following even prolonged, intensive and extensive application of the Ointment. The preparation is usually well tolerated by all age groups. It is not a primary irritant and apparently has only a slight sensitizing potential. However, it is well to remember that any oleaginous ointment vehicle may occasionally irritate when applied to moist, intertriginous areas.

Dosage and Administration: Fungizone (Amphotericin B) Cream, Lotion, or Ointment should be applied liberally to the candidal lesions two to four times daily. Duration of therapy depends on individual patient response. Intertriginous lesions usually respond within a few days, and treatment may be completed in one to three weeks. Similarly, candidiasis of the diaper area, perlecha, and glabrous skin lesions usually clear in one to two weeks. Interdigital (erosio) lesions may require two to four weeks of intensive therapy; paronychias also require relatively prolonged therapy, and those onychomycoses which respond may require several months or more of treatment. (Relapses are frequently encountered in the last three clinical conditions.)

NOTE: When rubbed into the lesion, the Cream discolors the skin minimally. The Lotion and Ointment do not stain the skin when thoroughly rubbed into the lesion although nail lesions may be stained. The patient should be informed that any discoloration of fabrics from the Cream may be removed by hand-washing the fabric with soap and warm water, that any discoloration of fabrics from the Lotion is readily removed with soap and warm water, or that any discoloration of fabrics from the Ointment may be removed by applying a standard cleaning fluid.

How Supplied: Fungizone Cream (Amphotericin B Cream USP) is supplied in tubes of 20 grams.

Fungizone Lotion (Amphotericin B Lotion USP) is supplied in 30 ml. plastic squeeze bottles (Military Depot Item, NSN 6505-00-890-1486).

Fungizone Ointment (Amphotericin B Ointment USP) is supplied in tubes of 20 grams.

Storage: Store the Cream and Lotion [illegible] temperature; avoid freezing. Store the Oi[illegible] at room temperature.

FUNGIZONE® INTRAVENOUS
(Amphotericin B for Injection USP)

WARNING

This drug should be used *primarily for* [illegible] ment of patients with progressive and po[illegible] tially fatal fungal infections; it should not [illegible] used to treat the common clinically inapp[illegible] ent forms of fungal disease which show [illegible] positive skin or serologic tests.

Description: Fungizone Intravenous (Amph[illegible] cin B for Injection USP) is an antifungal [illegible] derived from a strain of *Streptomyces* [illegible] Crystalline amphotericin B is insoluble in [illegible] therefore, the antibiotic is "solubilized" [illegible] addition of sodium desoxycholate to form [illegible] ture which provides a colloidal dispersion for [illegible] enteral administration.

Actions:

Microbiology

Amphotericin B shows a high order of [illegible] tivity against many species of fungi. *Histo[illegible] capsulatum, Coccidiodes immitis, Candi[illegible] cies, Blastomyces dermatitidis, Rhodotorula [illegible] tococcus neoformans, Sporotrichum schenck[illegible] cor mucedo,* and *Aspergillus fumigatus* [illegible] hibited by concentrations of amphotericin B [illegible] ing from 0.03 to 1.0 mcg./ml. *In vitro* The [illegible] otic is without effect on bacteria, rickett[illegible] viruses.

Clinical Pharmacology

Amphotericin B is fungistatic or fungi[illegible] pending on the concentration obtained [illegible] fluids and the susceptibility of the [illegible] drug probably acts by binding to sterols [illegible] gus cell membrane with a resultant [illegible] membrane permeability which allows leak[illegible] variety of small molecules. Mammalian cell [illegible] branes also contain sterols and it has been [illegible] gested that the damage to human cells [illegible] cells may share common mechanisms.

An initial intravenous infusion of 1 to [illegible] amphotericin B per day, gradually increa[illegible] 0.65 mg./kg. daily, produces peak plasma [illegible] trations of approximately 2 to 4 mcg./ml. [illegible] can persist between doses since the plasma [illegible] life of amphotericin B is about 24 hours. [illegible] recommended dosages, see the DOSAGE AND ADMINISTRATION section.) It has been [illegible] that amphotericin B is highly bound to [illegible] plasma proteins and is poorly dialyzable.

Amphotericin B is excreted very slowly [illegible] kidneys with two to five percent of a dose [illegible] being excreted in biologically active form [illegible] treatment is discontinued, the drug is [illegible] tected in the urine for at least seven days. [illegible] cumulative urinary output over a seven-day [illegible] amounts to approximately 40 percent of the [illegible] amount of drug infused.

Details of tissue distribution and possible [illegible] bolic pathways are not known.

Indications: Fungizone Intravenous [illegible] administered primarily to patients with [illegible] sive, potentially fatal infections. This [illegible] should not be used to treat the common [illegible] ent forms of fungal disease which show [illegible] tive skin or serologic tests.

Fungizone Intravenous (Amphotericin B [illegible] tion USP) is specifically intended to treat [illegible] coccosis (torulosis); North American [illegible] sis; the disseminated forms of monilial [illegible] domycosis, and histoplasmosis; [illegible] (phycomycosis) caused by species of the [illegible] *Mucor, Rhizopus, Absidia, Entomophthora, Basidiobolus;* sporotrichosis (*Sporothrix* [formerly *Sporotrichum schenckii*]); [illegible] (*Aspergillus fumigatus*).

Amphotericin B may be helpful in the [illegible] of American mucocutaneous leishmaniasis; [illegible] not the drug of choice in primary [illegible]

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...ore indolent mycoses.
...ation of Solutions: Reconstitute as
...An initial concentrate of 5 mg. ampho-
...B per ml. is first prepared by rapidly
...ing 10 ml. Sterile Water for Injection
...without a bacteriostatic agent directly into
...philized cake, using a sterile needle
...um diameter: 20 gauge) and syringe.
...the vial immediately until the colloidal
...is clear. The infusion solution, provid-
...mg. amphotericin B per ml., is then ob-
...by further dilution (1:50) with 5% Dex-
...Injection USP *of pH above 4.2.* The pH of
...ainer of Dextrose Injection should be
...ed before use. Commercial Dextrose
...usually has a pH above 4.2; however,
...below 4.2, then 1 or 2 ml. of buffer should
...ed to the Dextrose Injection before it is
...ilute the concentrated solution of am-
...cin B. The recommended buffer has the
...ic composition:

...ic sodium phosphate (anhydrous)	1.59 g.
...bic sodium ...sphate (anhydrous)	0.96 g.
...er for Injection	qs. 100.0 ml.

...ffer should be sterilized before it is ...the Dextrose Injection, either by fil-...through a bacterial retentive stone, ...membrane, or by autoclaving for 30 ...at 15 lb. pressure (121° C.).
...TION: **Aseptic technique must be ...observed in all handling,** since no ...ive or bacteriostatic agent is present ...antibiotic or in the materials used to ...it for administration. **All entries into ...or into the diluents must be made ...a sterile needle. Do not reconstitute ...saline solutions. The use of any dilu-...ent other than the ones recommended or ...presence of a bacteriostatic agent** (e.g., ...alcohol) **in the diluent may cause pre-...cipitation of the antibiotic. Do not use the ...concentrate or the infusion solution ...if there is any evidence of precipitation or ...matter in either one.**
...ne membrane filter may be used for ...ous infusion of amphotericin B; **how-...ever, the mean pore diameter of the filter ...must not be less than 1.0 micron in order ...to insure passage of the antibiotic disper-...sion.**
...**Supplied:** Fungizone Intravenous is sup-...vials as a sterile lyophilized cake ...may partially reduce to powder follow-...manufacture) providing 50 mg. amphoteri-...and 41 mg. sodium desoxycholate with ...sodium phosphates as a buffer. At the ...manufacture, the air in the container is ...by nitrogen.
...Prior to reconstitution, Fungizone ...ous (Amphotericin B for injection ...should be stored in the refrigerator, pro-...against exposure to light. The concen-...mg. amphotericin B per ml. after re-...tion with 10 ml. Sterile Water for In-...USP) may be stored in the dark, at ...perature for 24 hours, or at refrigera-...peratures for one week with minimal ...tency and clarity. Any unused mate-...ould then be discarded. Solutions pre-...intravenous infusion (0.1 mg. or less ...cin B per ml.) should be used ...after preparation and should be pro-...light during administration.

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HALCIDERM® CREAM 0.1% B
(Halcinonide Cream 0.1%)

Description: Halciderm Cream (Halcinonide Cream 0.1%) contains the active synthetic corticosteroid halcinonide. Chemically, halcinonide is (11β,16α)-21-Chloro-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene) bis-(oxy)] pregn-4-ene-3,20-dione.
Each gram of Halciderm Cream 0.1% (Halcinonide Cream 0.1%) contains 1 mg. halcinonide in a hydrophilic vanishing cream base consisting of propylene glycol, dimethicone 350, castor oil, cetearyl alcohol (and) ceteareth-20, propylene glycol stearate, white petrolatum, and purified water. This formulation is water-washable, greaseless, and nonstaining, with moisturizing and emollient properties.
Actions: Halciderm Cream (Halcinonide Cream 0.1%) is primarily effective because of its anti-inflammatory, antipruritic, and vasoconstrictive actions.
Indications: Halciderm Cream is indicated for relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.
Contraindication: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the cream.
Precautions: General—If irritation develops, the product should be discontinued and appropriate therapy instituted.
In the presence of an infection, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
If extensive areas are treated or if the occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants.
This preparation is not for ophthalmic use.
Usage in Pregnancy—Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not been absolutely established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids, in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Occlusive Dressing Technique—The use of occlusive dressing increases the percutaneous absorption of corticosteroids. For patients with extensive lesions, it may be preferable to use a sequential approach, occluding one portion of the body at a time. The patient should be kept under close observation if treated with the occlusive technique over large areas and over a considerable period of time. Occasionally, a patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped. Thermal homeostasis may be impaired if large areas of the body are covered. Use of the occlusive dressing should be discontinued if elevation of the body temperature occurs. Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary.
If infection develops, discontinue the use of the occlusive dressing and institute appropriate antimicrobial therapy.
Adverse Reactions: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning sensations, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.
Dosage and Administration: Apply Halciderm Cream (Halcinonide Cream 0.1%) to the affected area one to three times daily. Rub in gently.
Occlusive Dressing Technique: Particularly resistant lesions of chronic dermatoses such as psoriasis and neurodermatitis may require the use of Halciderm Cream (Halcinonide Cream 0.1%) under occlusive dressings. Gently rub a small amount of the cream into the lesion until it disappears. Reapply the preparation leaving a thin coating on the lesion and cover with a pliable nonporous film. The frequency of changing dressings is best determined on an individual basis. Good results have been obtained by applying Halciderm Cream (Halcinonide Cream 0.1%) under an occlusive dressing in the evening and removing the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional cream should be applied, without occlusion, during the day. Reapplication is essential at each dressing change.
How Supplied: Available in 15 g., 30 g., and 60 g. tubes.
Storage: Store at room temperature; avoid freezing and refrigeration.

HALOG® B
(Halcinonide)
CREAM/OINTMENT/SOLUTION

Description: Halog preparations contain the active synthetic corticosteroid halcinonide. The chemical name is (11β,16α)-21-Chloro-9-fluoro-11-hydroxy-16, 17-[(1-methylethylidene) bis-(oxy)] pregn-4-ene-3,20-dione.
Halog Cream 0.025% (Halcinonide Cream 0.025%) contains 0.25 mg. halcinonide per gram in a specially formulated cream base consisting of glyceryl monostearate NF XII, cetyl alcohol, cetyl esters wax, polysorbate 60, propylene glycol, dimethicone 350, and purified water. Halog Cream 0.1% (Halcinonide Cream 0.1%) contains 1 mg. halcinonide per gram in a specially formulated cream base consisting of glyceryl monostearate NF XII, cetyl alcohol, isopropyl palmitate, dimethicone 350, polysorbate 60, titanium dioxide, propylene glycol, and purified water.
Halog Ointment 0.025% (Halcinonide Ointment 0.025%) contains 0.25 mg. halcinonide per gram in Plastibase® (Plasticized Hydrocarbon Gel), a polyethylene and mineral oil gel base with polyethylene glycol 400, polyethylene glycol 6000 distearate, polyethylene glycol 300, polyethylene glycol 1540, and butylated hydroxytoluene as a preservative. Halog Ointment 0.1% (Halcinonide Ointment 0.1%) contains 1 mg. halcinonide per gram in Plastibase® (Plasticized Hydrocarbon Gel), a polyethylene and mineral oil gel base with polyethylene glycol 400, polyethylene glycol 6000 distearate, polyethylene glycol 300, polyethylene glycol 1540, and butylated hydroxytoluene as a preservative.
Halog Solution 0.1% (Halcinonide Solution 0.1%) contains 1 mg. halcinonide (0.1%) per mL with edetate disodium, polyethylene glycol 300, purified water, and butylated hydroxytoluene as a preservative.
Actions: Halcinonide preparations are primarily effective because of their anti-inflammatory, antipruritic and vasoconstrictive actions.
Indications: Halog (Halcinonide) preparations are indicated for relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.
Contraindication: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

Continued on next page

...tor...ge: Store the Cream and Lotion ...emperature; avoid freezing. Store the ... at room temperature.

FUNGIZONE® INTRAVENOUS
(Amphotericin B for Injection USP)

WARNING

This drug should be used *primarily* ... ment of patients with progressive and ... tially fatal fungal infections; it should ... used to treat the common clinically ... ent forms of fungal disease which ... positive skin or serologic tests.

Description: Fungizone Intravenous (... cin B for Injection USP) is an antifungal ... derived from a strain of *Streptomyces*. ... Crystalline amphotericin B is insoluble ... therefore, the antibiotic is "solubilized" ... addition of sodium desoxycholate to ... ture which provides a colloidal dispersion ... enteral administration.

Actions:

Microbiology

Amphotericin B shows a high order of ... tivity against many species of fungi, ... *capsulatum, Coccidiodes immitis, C...* cies, *Blastomyces dermatitidis, Rhodo... tococcus neoformans, Sporotrichum s... cor mucedo,* and *Aspergillus fumigatus*. ... hibited by concentrations of amphoteri... ing from 0.03 to 1.0 mcg./ml. *in vitro*. ... otic is without effect on bacteria, ... viruses.

Clinical Pharmacology

Amphotericin B is fungistatic or fun... pending on the concentration obtain... fluids and the susceptibility of the ... drug probably acts by binding to sterol... gus cell membrane with a resultant ... membrane permeability which allows ... variety of small molecules. Mammalian ... branes also contain sterols and it has ... gested that the damage to human cell... cells may share common mechanism...

An initial intravenous infusion of ... amphotericin B per day, gradually ... 0.65 mg./kg. daily, produces peak plas... trations of approximately 2 to 4 mcg./... can persist between doses since the ... life of amphotericin B is about 24 ... recommended dosages, see the DOSAGE AND ADMINISTRATION section.) It has been ... that amphotericin B is highly bound ... plasma proteins and is poorly dialyzable. ... Amphotericin B is excreted very slowly ... kidneys with two to five percent of ... being excreted in biologically active ... treatment is discontinued, the drug ... tected in the urine for at least seven ... cumulative urinary output over a seven ... amounts to approximately 40 percent ... amount of drug infused.

Details of tissue distribution and ... bolic pathways are not known.

Indications: Fungizone Intravenous ... administered primarily to patients ... sive, potentially fatal infections. This ... should not be used to treat the common ... ent forms of fungal disease which show ... tive skin or serologic tests.

Fungizone Intravenous (Amphotericin ... tion USP) is specifically intended for ... coccosis (torulosis); North American ... sis; the disseminated forms of monilial ... domycosis, and histoplasmosis; and ... (phycomycosis) caused by species of ... *Mucor, Rhizopus, Absidia, Entomo... Basidiobolus;* sporotrichosis (*Sporo... [formerly Sporotrichum schenckii*); ... (*Aspergillus fumigatus*).

Amphotericin B may be helpful in ... of American mucocutaneous leishm... not the drug of choice in primary ...

Contraindications: This product is contraindi... those patients who have shown hypersen... unless, in the opinion of the physician, ... condition requiring treatment is life-threaten... amenable only to amphotericin B therapy. ... Amphotericin B is frequently the only ... treatment available for potentially fatal ... disease. In each case, its possible life-saving ... must be balanced against its untoward and ... side effects.

Pregnancy: Safety for use in pregnancy ... been established; therefore, it should be ... during pregnancy only if the possible benefits ... derived outweigh the potential risks in...

Precautions: Prolonged therapy with amphoteri... usually necessary. Unpleasant reactions ... common when the drug is given paren... therapeutic dosage levels. **Some of ... reactions are potentially dangerous.** ... Amphotericin B should be used parenter... in hospitalized patients or those under ... clinical observation by medically trained ... and should be reserved for those pa... in whom a diagnosis of the progressive, po... fatal forms of susceptible mycotic infec... been firmly established, preferably by ... culture or histologic study.

Steroids should not be administered con... unless they are necessary to control ... tions. Other nephrotoxic antibiotics and ... toxic agents such as nitrogen mustard ... not be given concomitantly except with ... ation.

...ory facilities must be available to perform ... nitrogen and serum creatinine or en... creatinine clearance tests. These deter... should be made at least weekly during ... If the BUN exceeds 40 mg. per 100 ml. or ... creatinine exceeds 3.0 mg. per 100 ml. ... should be discontinued or the dosage ... reduced until renal function is im... Weekly hemograms and serum potassium ... tions are also advisable. Low serum ... levels have also been noted during ... with amphotericin B. Therapy should ... continued if liver function test results (ele... sulphalein, alkaline phosphatase and ... are abnormal.

If medication is interrupted for a period ... in seven days, therapy should be re... starting with the lowest dosage level, ... mg./kg. of body weight, and increased ... as outlined under DOSAGE AND AD... ATION.

Adverse Reactions: While some few patients ... full intravenous doses of amphoteri... without difficulty, most will exhibit some ... often at less than the full therapeutic ... may be made less severe by giving ... antihistamines, and antiemetics. Admin... of the drug on alternate days may de... thrombophlebitis and phlebitis. Intravenous admin... small doses of adrenal corticosteroids ... or during the amphotericin B infusion ... febrile reactions. The dosage and ... such corticosteroid therapy should be ... minimum. Adding a small amount of ... to the infusion may lessen the incidence of ... phlebitis. Extravasation may cause chem...

The adverse reactions that are most commonly ... chills, fever (sometimes with shaking ... headache; anorexia; weight loss; nausea ... vomiting; malaise; dyspepsia; diarrhea; gener... pain including muscle and joint pains, ... pain, gastric pain, and local venous pain at ... site with phlebitis and thrombophle... normochromic, normocytic anemia. ... renal function including hypokalemia, ... hyposthenuria, renal tubular acidosis ... hypocalcinosis is also commonly observed, ... improves upon interruption of ther... some permanent impairment often ... especially in those patients receiving large ... (over 5 g.) of amphotericin B. Supplemen... medication may decrease renal tubular ... complications.

The following adverse reactions occur less frequently or rarely: anuria; oliguria; cardiovascular toxicity including arrhythmias, ventricular fibrillation, cardiac arrest, hypertension, and hypotension; coagulation defects; thrombocytopenia; leukopenia; agranulocytosis; eosinophilia; leukocytosis; melena or hemorrhagic gastroenteritis; maculopapular rash; hearing loss; tinnitus; transient vertigo; blurred vision or diplopia; peripheral neuropathy; convulsions and other neurologic symptoms; pruritus (without rash); anaphylactoid reactions; acute liver failure; and flushing.

Dosage and Administration: Fungizone Intravenous (Amphotericin B for Injection USP) should be administered by *slow* intravenous infusion. Intravenous infusion should be given over a period of approximately six hours observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0.1 mg./ml. (1 mg./10 ml.).

Dosage must be adjusted to the specific requirements of each patient since tolerance to amphotericin B varies individually. Therapy is usually instituted with a daily dose of 0.25 mg./kg. of body weight and **gradually** increased as tolerance permits. There are insufficient data presently available to define total dosage requirements and duration of treatment necessary for eradication of mycoses such as phycomycosis. The optimal dose is unknown. Total daily dosage may range up to 1.0 mg./kg. of body weight or alternate day dosages ranging up to 1.5 mg./kg. Several months of therapy are usually necessary; a shorter period of therapy may produce an inadequate response and lead to relapse.

CAUTION: Under no circumstances should a total daily dosage of 1.5 mg./kg. be exceeded.

Therapy with intravenous amphotericin B for sporotrichosis has ranged up to nine months. The usual dose per injection is 20 mg.

Aspergilloeis has been treated with amphotericin B intravenously for a period up to 11 months with a total dose up to 3.6 g.

Rhinocerebral phycomycosis, a fulminating disease, generally occurs in association with diabetic ketoacidosis. It is, therefore, imperative that rapid restoration of diabetic control be instituted before successful treatment with Fungizone Intravenous (Amphotericin B for Injection USP) can be accomplished. In contradistinction, pulmonary phycomycosis, which is more common in association with hematologic malignancies, is often an incidental finding at autopsy. A cumulative dose of at least 3 g. of amphotericin B is recommended. Although a total dose of 3 to 4 g. will infrequently cause lasting renal impairment, this would seem a reasonable minimum where there is clinical evidence of invasion of the deep tissues; since rhinocerebral phycomycosis usually follows a rapidly fatal course, the therapeutic approach must necessarily be more aggressive than that used in more indolent mycoses.

Preparation of Solutions: Reconstitute as follows: An initial concentrate of 5 mg. amphotericin B per mL. is first prepared by rapidly expressing 10 ml. Sterile Water for Injection USP *without a bacteriostatic agent* directly into the lyophilized cake, using a sterile needle (minimum diameter: 20 gauge) and syringe. Shake the vial immediately until the colloidal solution is clear. The infusion solution, providing 0.1 mg. amphotericin B per ml., is then obtained by further dilution (1:50) with 5% Dextrose Injection USP *of pH above 4.2*. The pH of each container of Dextrose Injection should be ascertained before use. Commercial Dextrose Injection usually has a pH above 4.2; however, if it is below 4.2, then 1 or 2 ml. of buffer should be added to the Dextrose Injection before it is used to dilute the concentrated solution of amphotericin B. The recommended buffer has the following composition:

Dibasic sodium phosphate (anhydrous)	1.59 g.
Monobasic sodium phosphate (anhydrous)	0.96 g.
Water for Injection USP	qs. 100.0 mL

The buffer should be sterilized before it is added to the Dextrose Injection, either by filtration through a bacterial retentive stone, mat, or membrane, or by autoclaving for 30 minutes at 15 lb. pressure (121° C.).

CAUTION: Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in the antibiotic or in the materials used to prepare it for administration. **All entries into the vial or into the diluents must be made with a sterile needle. Do not reconstitute with saline solutions. The use of any diluent other than the ones recommended or the presence of a bacteriostatic agent** (e.g., benzyl alcohol) **in the diluent may cause precipitation of the antibiotic. Do not use the initial concentrate or the infusion solution if there is any evidence of precipitation or foreign matter in either one.**

An in-line membrane filter may be used for intravenous infusion of amphotericin B; **however, the mean pore diameter of the filter should not be less than 1.0 micron in order to assure passage of the antibiotic dispersion.**

How Supplied: Fungizone Intravenous is supplied in vials as a sterile lyophilized cake (which may partially reduce to powder following manufacture) providing 50 mg. amphotericin B and 41 mg. sodium desoxycholate with 20.2 mg. sodium phosphates as a buffer. At the time of manufacture, the air in the container is replaced by nitrogen. [Military Depot Item: NSN 6505-01-084-9453.]

Storage: Prior to reconstitution, Fungizone Intravenous (Amphotericin B for injection USP) should be stored in the refrigerator, protected against exposure to light. The concentrate (5 mg. amphotericin B per ml. after reconstitution with 10 ml. Sterile Water for Injection USP) may be stored in the dark, at room temperature for 24 hours, or at refrigerator temperatures for one week with minimal loss of potency and clarity. Any unused material should then be discarded. Solutions prepared for intravenous infusion (0.1 mg. or less amphotericin B per ml.) should be used promptly after preparation and should be protected from light during administration.

HALCIDERM® CREAM
(Halcinonide Cream 0.1%)

Description: The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The steroids in this class include halcinonide. Halcinonide is designated chemically as 21-Chloro-9-fluoro-11β, 16α,17-trihydroxypregn-4-ene-3,20-dione cyclic 16,17-acetal with acetone.

Each gram of 0.1% Halciderm Cream (Halcinonide Cream) contains 1 mg. halcinonide in a hydrophilic vanishing cream base consisting of propylene glycol, dimethicone 350, castor oil, cetearyl alcohol (and) ceteareth-20, propylene glycol stearate, white petrolatum, and purified water. This formulation is water-washable, greaseless, and nonstaining, with moisturizing and emollient properties.

Clinical Pharmacology: Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other dis-

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